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The Azomethine Ylid Strategy in β-Lactam Synthesis. Application to Selenapenams

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Abstract—Using azomethine ylid reactivity available from the β-lactam-based oxazolidinone **1**, selenoketones **6a–e** react as 1,3-dipolarophiles to give racemic selenapenams **7a–e** in a single step. The cycloaddition sequence proceeds with complete control of regiochemistry and the thermodynamically more stable *C*(3)/*C*(5) relationship is observed. The selenothiocarboxylate **9a** and the selenocarboxylate **9b** also function as effective dipolarophiles, but attempts to convert the resulting cycloadducts **10a** and **10b** to the corresponding selenapenems were unsuccessful. Other selenium-containing dipolarophiles failed to give characterizable cycloadducts.

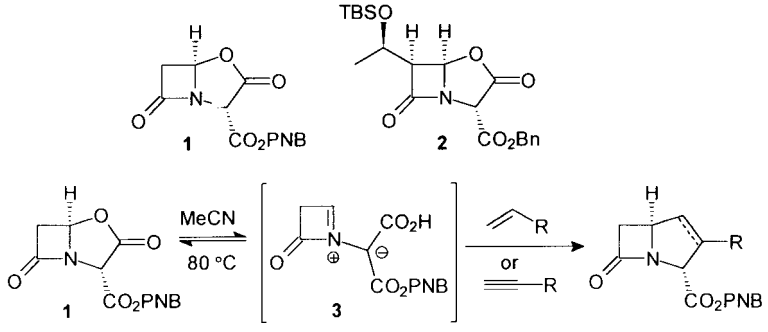
Introduction

We have recently described a novel synthetic strategy for the assembly of a variety of bicyclic β-lactam skeletons.[1–3] This is based on establishing the 1-azabicyclo[3.2.1]heptane skeleton using a 1,3-dipolar cycloaddition reactions involving an azomethine ylid derived from either the simple oxazolidinone **1** or the more highly functionalised variant **2**.[4]

Thermolysis of, for example, **1** (PNB=$CH_2C_6H_4$-4-NO_2) provides access to the key 1,3-dipole, which has been formulated as the carboxyl stabilized variant **3**, and this species undergoes addition to both alkenes and alkynes to generate carbapenams and Δ^1-carbapenems in a single step (Scheme 1).

Given the highly convergent nature of the chemistry outlined in Scheme 1, and the equally important role played by both the 4π and 2π components, an ability to harness a wide range of dipolarophiles is a critical element in determining the overall scope and utility of the azomethine ylid strategy. We have exploited this opportunity to vary the structure of the 1,3-dipolarophile component with a particular interest in 2π components containing a heteroatom moiety. Dipolarophiles incorporating heteroatoms offer access to a variety of important (and also novel) β-lactam derivatives, and use of carbonyl and thiocarbonyl-based dipolarophiles provides entries to oxapenams,[5] 2-substituted penams, and both *endo*- and *exo*-penems, respectively[1] (Scheme 2).

As part of this program, we have now extended the range of



Scheme 1.

Keywords: selenapenams; β-lactam; selenoketones; azomethine ylid.
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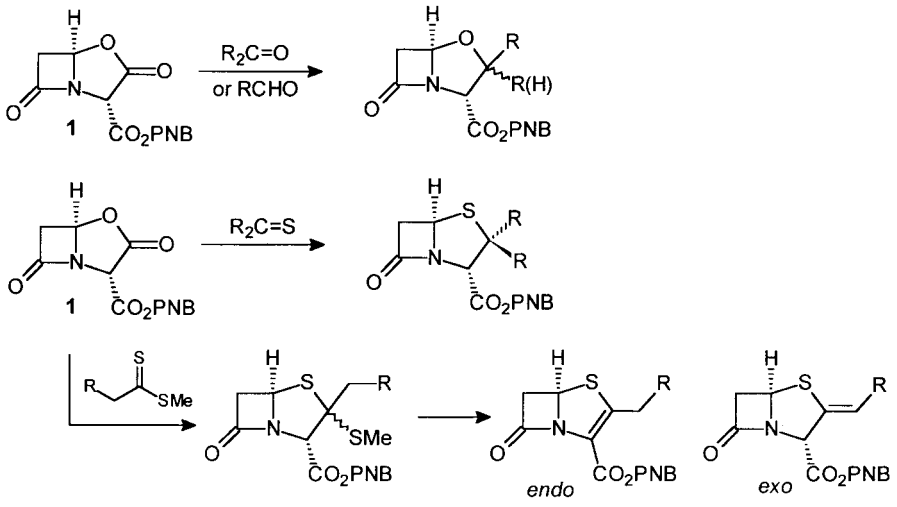


Scheme 2.

Group VI dipolarophiles that have been investigated to encompass selenocarbonyl variants. In this paper we describe the reactivity of various C=Se containing dipolarophiles towards the β-lactam based azomethine ylid **3**, and the successful extension of this cycloaddition strategy to the synthesis of selenapenams.

Results and Discussion

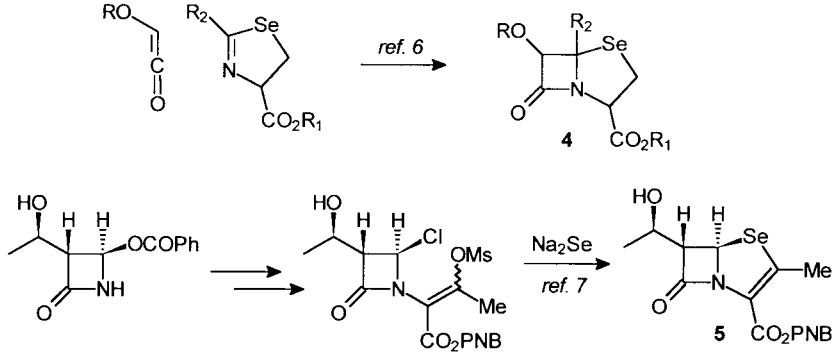
As a class of β-lactam derivatives, selenapenams and selenapenems have received only very limited attention (Scheme 3). To date, only one report of the synthesis of selenapenams **4** (but lacking a *C*(2) substituent) has appeared (in a patent[6]) based on the use of the Staudinger reaction. Similarly, Perrone et al.,[7] have described the only entry to selenapenems **5**, together with an evaluation of the antibacterial activity of this novel ring system, which resembled the corresponding penem.

Our approach to the construction of selenapenams and selenapenems has been based on the experience that we gained via the corresponding sulfur variants. The results reported in this paper have arisen from an evaluation of a series of selenoketones, as well as a number of other, more highly oxidised variants as 1,3-dipolarophiles towards the azomethine ylid derived from the β-lactam derivative **1**.

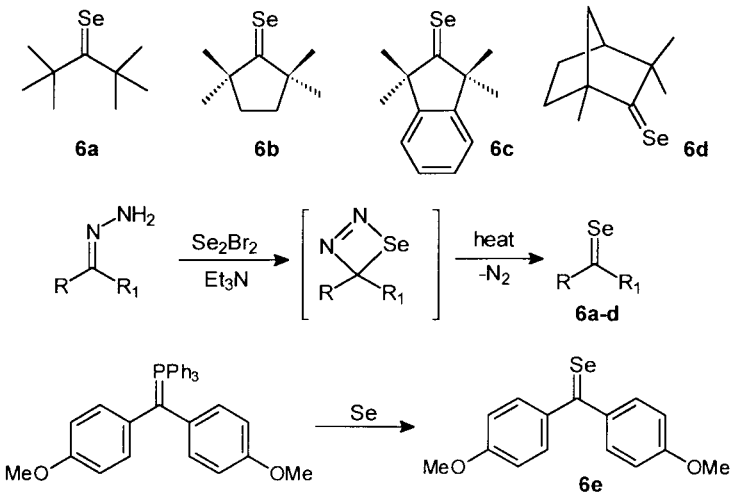
Use of selenoketones as dipolarophiles; synthesis and characterization of selenapenams

Selenoketones represent a reactive class of carbonyl derivatives, but highly hindered derivatives are sufficiently stable to isolate and to use as both dienophiles and dipolarophiles.[8] We have prepared a series of selenoketones **6a–e** using established methods (Scheme 4). The dialkyl variants **6a–d** were generated from the corresponding hydrazone with Se_2Br_2, followed by thermolysis.[9] The diaryl derivative **6e** was obtained by the method of Okuma[10] by reaction of the corresponding benzylic ylid with elemental selenium, followed by purification by rapid chromatography.

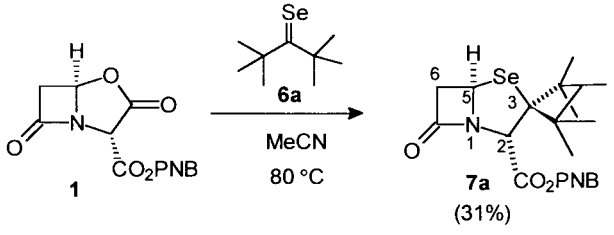
While selenoketones have found limited application as 1,3-dipolarophiles,[11–16] thermolysis of oxazolidinone **1** in the presence of selenoketones **6a–e** proceeded smoothly and the corresponding racemic selenapenams **7a–e** were isolated following chromatography (see Scheme 5 and Table 1). The yields of cycloadducts obtained are moderate (25 to 37%), but it is also important to appreciate (i) the relative instability of these selenium-based dipolarophiles and (ii) that this process provides novel selenapenams in a *single* step in a regio and stereochemically defined manner. In the case of the (1*R*)-fenchone-derived cycloadduct **7d**, a separable 1:1.3 mixture of two isomeric adducts (the stereochemistry of which has not been fully assigned) was obtained.



Scheme 3.



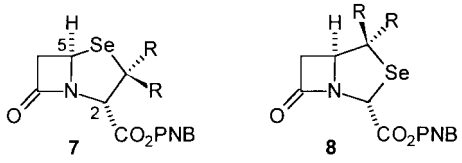
Scheme 4.



Scheme 5.

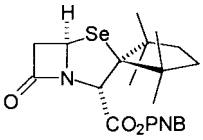
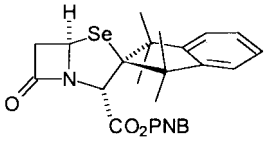
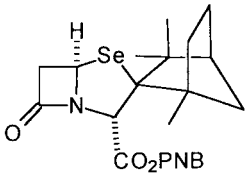
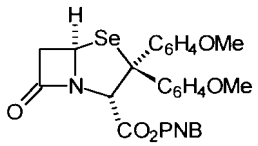
There are a number of structural aspects associated with selenapenams **7a**–**e** that merit discussion. While we were unable to obtain suitable crystals for X-ray crystallographic analysis (however, see below), assignment of regiochemistry (selenapenam **7** vs. isoselenapenam **8**) was achieved by NMR spectroscopy, based on comparison with structurally related penams and, more directly, by examination of the $^{1}H/^{77}Se$ correlation spectra (see Fig. 1). In the case of selenapenam **7a**, couplings to the selenium signal (at δ 523.2) were observed with both *H*(5) and the two diastereotopic *H*(6) protons. No correlation to *H*(2) was detected. For **7a**, *H*(5) appeared as doublet of doublets of doublets ($^{2}J_{H(5),Se}$=17 Hz, $^{3}J_{H(5),H(6)}$=1.5 Hz, $^{3}J_{H(5),H(6)}$= 4 Hz). Similarly, *C*(5) (δ 55.2) showed a $^{1}J_{C,Se}$ value of 86 Hz.[17]

These observations are consistent with the selenapenam regiochemistry rather than the alternative structure **8**. The NOE data described below are also in agreement with this conclusion.



The relative stereochemistry at *C*(2) was assigned (again in the case of cycloadduct **7a**) by NOE difference spectroscopy: irradiation of *H*(2) showed no enhancement of *H*(5), but the signals due to the *tert*-Bu group were enhanced. Similar observations (which have also been confirmed by X-ray crystallographic analysis) were exploited in order to assign the regiochemical outcome of

Table 1.

Selenoketone	Selenapenam (% yield)	Selenoketone	Selenapenam (% yield)
6b	 **7b** (30 %)	**6c**	 **7c** (37 %)
6d	 **7d** (29 %)	**6e**	 **7e** (25 %)

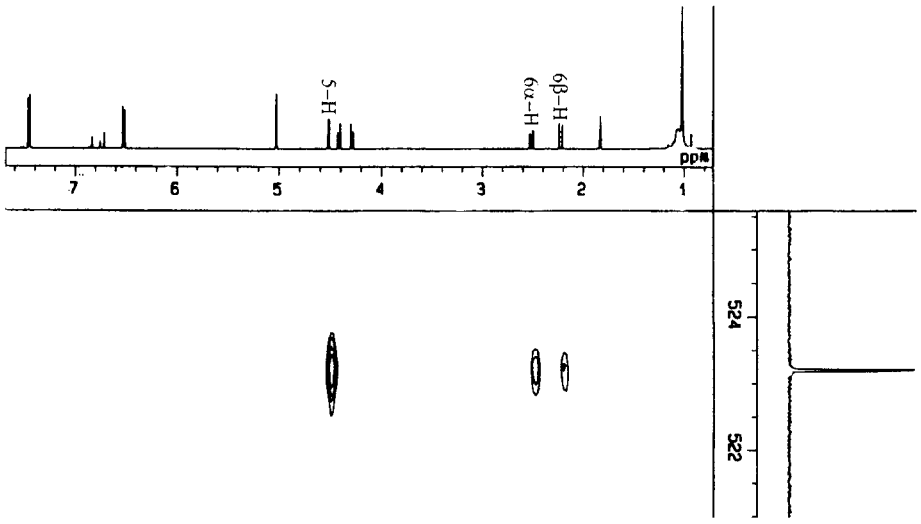


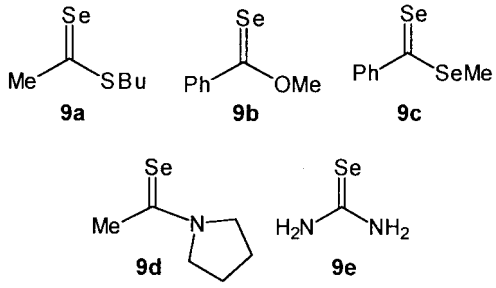
Figure 1. $^{1}H/^{77}Se$ correlation spectrum (rt, d^8 toluene) of selenapenam **7a**.

cycloaddition reactions leading to oxapenams and penams, and the *C*(2)/*C*(5) stereochemistry shown in cycloadducts **7** is anticipated to correspond to the thermodynamically more favored arrangement.[5]

The steric bulk associated with selenoketones **6** and how this might inhibit the cycloaddition process was a concern, and this factor may contribute in part of the moderate yields that were observed. However, the demands associated with sterically congested 3,3-disubstituted selenapenams were evident nevertheless. At room temperature, the ^{1}H NMR spectrum of the 3,3-bis(*tert*-butyl) cycloadduct **7a** showed significant broadening of the peaks corresponding to the diastereotopic *tert*-Bu residues. At low temperature (−60°C) the six methyl groups are cleanly resolved, and at +60°C free rotation is possible and two distinct and sharper singlets are observed (Fig. 2).

Alternative C═Se based dipolarophiles

We have successfully applied dithioesters and trithiocarbamates to the synthesis of 3-alkyl (and 3-aryl) penems, and 3-thioalkyl penems, respectively.[1] With this in mind, a number of other selenium-containing derivatives **9a–e**[18–21] have been evaluated as dipolarophiles.



As shown in Scheme 6, oxazolidinone **1** underwent thermal reaction with both **9a** and **9b** to give the corresponding cycloadducts **10a** (1:1) and **10b** (2:1) respectively and in both cases mixtures of diastereoisomers were obtained. In the case of adduct **10b**, the major isomer was crystallized

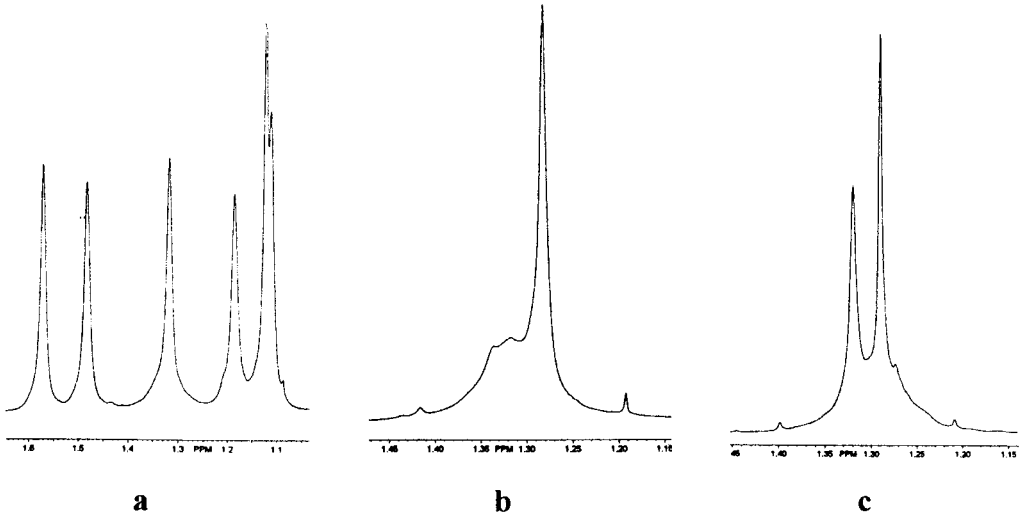
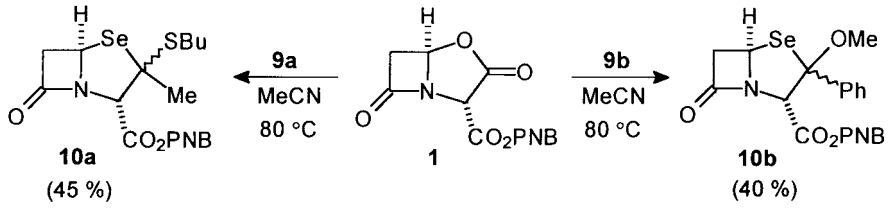


Figure 2. ^{1}H NMR spectra of selenapenam **7a** at: (a) −60°C; (b) room temperature; (c) +60°C.



Scheme 6.

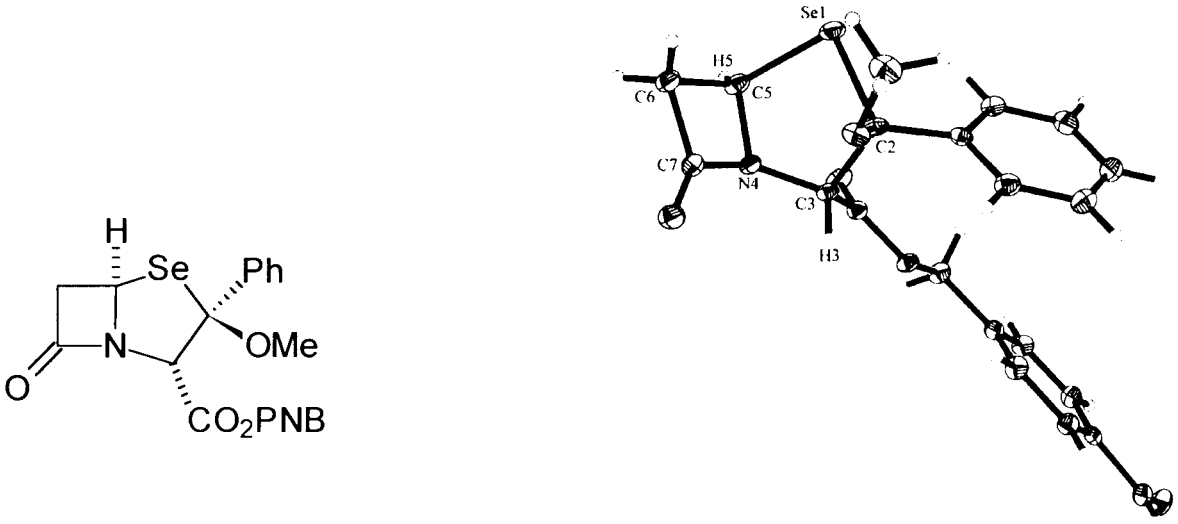
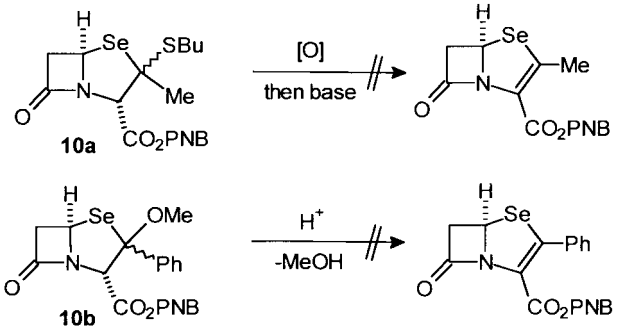


Figure 3. Ellipsoid diagram of **10b** (major isomer).

(from the mixture) and the structure was confirmed by X-ray crystallographic analysis (Fig. 3).[22]

Somewhat surprisingly, the diselenoester **9c** failed to give a cycloadduct—**9c** underwent extensive decomposition (elemental selenium precipitated) under the reaction conditions used—and neither the selenoamide **9d** nor selenourea **9e** gave a characterizable product. In the corresponding sulfur series, we had also found that thioamides and thioureas are not effective dipolarophiles towards the β-lactam-based azomethine ylid **3**.

Attempts were also made to convert cycloadducts **10a** and **10b** to the corresponding selenapenems, but without success (Scheme 7). Using the protocols derived from our earlier entry to penems,[1] attempts to achieve an *S*-selective oxidation of **10a** (using either mCPBA or H_2O_2) failed and a complex mixture of products was obtained. While in the penem series we do observe a high kinetic preference for oxidation of the acyclic rather than the heterocyclic sulfur atom, the presence of the more reactive selenium center compromises this approach. Using cycloadduct **10b**, a different approach was examined. However, attempts to achieve an overall elimination of methanol using a variety of acid catalysed conditions (using either PPTS or HBF_4) failed despite the benzylic nature of the leaving group.



Scheme 7.

In summary, the azomethine ylid strategy for bicyclic β-lactam synthesis provides a direct entry into a range of bicyclic selenium-containing derivatives. Selenapenams are available using selenoketones as dipolarophiles, and the cycloaddition process proceeds with complete regiochemical control. These selenium-based 2π components have not been widely exploited as dipolarophiles and this chemistry opens the way towards more general application of these units in 1,3-dipolar cycloaddition chemistry.[23] Reactive selenothioesters and selenoesters also function as viable dipolarophiles towards the β-lactam based azomethine ylid, but to date we have been unsuccessful in converting the resulting cycloadducts into selenapenems.

Experimental

Infrared spectra (ν_{max}) were recorded using a Perkin–Elmer 1715 FTIR spectrometer, in the range of 4000–600 cm^{-1}

either as a neat film on NaCl plates or as a solution in CH_2Cl_2, using NaCl solution cells. Mass spectra *m/z* (E.I., C.I.) were obtained using a Fisons/VG Analytical Autospec System. Nuclear magnetic resonance (NMR) spectra were recorded at the field strength and in the solvent indicated using standard pulse sequences on a Alpha 500, Jeol GX400 or a Lambda 300. Chemical shifts are expressed in ppm (δ) and are referenced to Me_4Si. Proton and carbon assignments were made using a combination of $^1H/^1H$ and $^1H/^{13}C$ correlation spectra and ^{77}Se NMR are externally referenced to Me_2Se. Coupling constants (*J*) are quoted in Hz. All commercially available reagents and solvents were purified and dried according to standard procedures and all yields refer to isolated materials homogeneous by TLC and ^1H NMR unless stated. The numbering system of the β-lactam units used (see structure **7a**, Scheme 5) corresponds to the nomenclature used below.

(2*S,5*R**)-7-Oxo-3,3-bis(*tert*-butyl)-4-selena-1-azabicyclo[3.2.1]heptane-2-carboxylic acid PNB ester 7a**. A solution of oxazolidinone **1** (0.277 g, 0.90 mmol) and selenoketone **6a** (0.204 g, 0.99 mmol) in MeCN (6 cm^3) [distilled and degassed] was heated at 80°C for 15 h in a sealed tube. The solvent was removed in vacuo and the residue was purified by flash column chromatography [60H silica gel, 1:9→1:5 EtOAc–P.E. 40–60°C] to give selenopenam **7a** (0.132 g, 31%) as a pale yellow solid mp 143–145°C (CH_2Cl_2/*n*-pentane) (Found: $M+H^+$, 463.1301. $C_{21}H_{29}N_2O_5{}^{74}Se$ requires 463.1301); *m/z* (E.I.) 396 (6%); (C.I.) (^{80}Se) 497 ($M+C_2H_5^+$, 5%), 467 ($M+H^+$, 1); ν_{max} (CH_2Cl_2)/cm^{-1} 1771, 1752; δ_H (300 MHz: C_6D_6) 1.15 (9H, br. s, 3×CH_3), 1.35 (9H, br. s, 3×CH_3), 2.25 (1H, dd, *J*=15.5, 1.5 Hz, 6β-H), 2.53 (1H, dd, *J*=15.5, 4.0 Hz, 6α-H), 4.32 (1H, part of AB, *J*=13.0 Hz, CH_2Ar), 4.45 (1H, part of AB, *J*=13.0 Hz, CH_2Ar), 4.55 (1H, dd, *J*=4.0, 1.5 Hz, 5-H), 5.07 (1H, s, 2-H), 6.55 (2H, part of AA′BB′, *J*=8.5 Hz, Ar) and 7.51 (2H, part of AA′BB′, *J*=8.5 Hz, Ar); δ_C (75.5 MHz: C_6D_6) 30.3 (*C*H_3), 33.3 (br, 5×*C*H_3), 44.0 ($C_{quat.}$), 44.1 ($C_{quat.}$), 45.1 (6-*C*H_2), 55.2 (5-*C*H), 65.2 (2-*C*H), 66.0 (*C*H_2Ar), 102.2 ($C_{quat.}$), 123.8 (CH), 128.7 (CH), 141.8 (C_{ipso}), 148.1 (C_{ipso}), 170.0 (C═O) and 170.9 (C═O); δ_{Se} (95.35 MHz: $C_6D_6CD_3$) 523.2.

(2′*S,5′*R**)-7′-Oxo-2,2,5,5-tetramethylspiro[cyclopentane-1,3′-[4]selena[1]azabicyclo[3.2.0]heptane]-2′-carboxylic acid PNB ester 7b.** A solution of oxazolidinone **1** (0.055 g, 0.18 mmol) and selenoketone **6b** (0.038 g, 0.19 mmol) in MeCN (2 cm^3) [distilled and degassed] was heated at 80°C for 15 h in a sealed tube. The solvent was removed in vacuo and the residue was purified by flash column chromatography [60H silica gel, 1:9→1:5 EtOAc–P.E. 40–60°C] to give selenopenam **7b** (0.026 g, 30%) as a pale yellow oil (Found: $M+H^+$, 461.1149. $C_{21}H_{27}N_2O_5{}^{74}Se$ requires 461.1145); *m/z* (E.I.) (^{80}Se) 466 ($M+H^+$, 7%); (C.I.) (^{80}Se) 466 ($M+H^+$, 24%); ν_{max} (CH_2Cl_2)/cm^{-1} 1769, 1747, 1607; δ_H (300 MHz: CD_3CN, rt) 1.20 (3H, s, CH_3), 1.23 (3H, s, CH_3), 1.28 (3H, s, CH_3), 1.37 (3H, s, CH_3), 1.47–1.67 (4H, m, 2×CH_2), 3.12 (1H, dd, *J*=16.0, 2.0 Hz, 6′β-H), 3.53 (1H, dd, *J*=16.0, 4.0 Hz, 6′α-H), 4.92 (1H, s, 2′-H), 5.28 (2H, s, CH_2Ar), 5.39 (1H, dd, *J*=4.0, 2.0 Hz, 5′-H), 7.65 (2H, part of AA′BB′, *J*=9.0 Hz, Ar) and 8.23 (2H, part of AA′BB′, *J*=9.0 Hz, Ar); δ_C (75.5 MHz: CD_3CN) 27.5 (*C*H_3), 28.8 (*C*H_3), 33.3 (*C*H_3), 34.9 (*C*H_3), 39.3 (*C*H_2), 43.2 (*C*H_2), 47.1 ($C_{quat.}$), 47.4 (6′-*C*H_2), 48.2 ($C_{quat.}$), 53.6 (5′-*C*H), 63.1 (2′-*C*H), 65.4 (*C*H_2Ar), 94.6 ($C_{quat.}$), 123.7 (CH), 128.5 (CH), 141.6 (C_{ipso}), 148.0 (C_{ipso}), 167.8 (C═O) and 167.9 (C═O).

(2′*S,5′*R**)-7′-Oxo-2,2,5,5-tetramethylspiro[indane-1,3′-[4]selena[1]azabicyclo[3.2.0]heptane]-2′-carboxylic acid PNB ester 7c.** A solution of oxazolidinone **1** (0.252 g, 0.82 mmol) and selenoketone **6c** (0.240 g, 0.92 mmol) in MeCN (5 cm^3) [distilled and degassed] was heated at 80°C for 18 h in a sealed tube. The solvent was removed in vacuo and the residue was purified by flash column chromatography [60H silica gel, 1:9→1:5 EtOAc–P.E. 40–60°C] to give selenopenam **7c** (0.160 g, 37%) as a colorless solid mp 155–157°C (benzene/pentane) (Found: M^+, 514.1018. $C_{25}H_{26}N_2O_5{}^{80}Se$ requires 514.1007); *m/z* (E.I.) (^{80}Se) 514 (M^+, 2%); ν_{max} (CH_2Cl_2)/cm^{-1} 1774, 1746; δ_H (270 MHz: CD_2Cl_2) 1.34 (3H, s, CH_3), 1.52 (3H, s, CH_3), 1.61 (3H, s, CH_3), 1.67 (3H, s, CH_3), 3.12 (1H, dd, *J*=16.0, 2.0 Hz, 6′β-H), 3.60 (1H, dd, *J*=16.0, 4.0 Hz, 6′α-H), 4.83 (1H, part of AB, *J*=13.0 Hz, CH_2Ar), 5.07 (1H, s, 2′-H), 5.12 (1H, part of AB, *J*=13.0 Hz, CH_2Ar), 5.44 (1H, dd, *J*=4.0 Hz, 2.0, 5′-H), 7.01–7.09 (2H, m, Ar), 7.11–7.22 (2H, m, Ar), 7.41 (2H, part of AA′BB′, *J*=9.0 Hz, Ar), and 8.17 (2H, part of AA′BB′, *J*=9.0 Hz, Ar); δ_C (75.5 MHz: CD_2Cl_2) 28.4 (*C*H_3), 28.7 (*C*H_3), 34.3 (*C*H_3), 35.5 (*C*H_3), 45.8 (6′-*C*H_2), 51.1 ($C_{quat.}$), 51.3 ($C_{quat.}$), 52.3 (5′-*C*H), 66.1 (2′-*C*H), 66.3 (*C*H_2Ar), 93.5 ($C_{quat.}$), 121.8 (CH), 122.5 (CH), 124.2 (CH), 127.5 (CH), 127.7 (CH), 129.4 (CH), 142.6 (C_{ipso}), 148.4 (C_{ipso}), 148.6 (C_{ipso}), 150.4 (C_{ipso}), 168.2 (C═O) and 171.1 (C═O).

(1*R*)-7′-Oxo-1,3,3-trimethylspiro[bicyclo[2.2.1]heptane-1,3′-[4]selena[1]azabicyclo[3.2.0]heptane]-2′-carboxylic acid PNB ester 7d. A solution of oxazolidinone **1** (0.062 g, 0.20 mmol) and selenoketone **6d** (0.045 g, 0.21 mmol) in MeCN (2 cm^3) [distilled and degassed] was heated at 80°C for 18 h in a sealed tube. The solvent was removed in vacuo and the residue was purified by flash column chromatography [60H silica gel, 1:9→1:4 EtOAc–P.E. 40–60°C] to give selenopenam **7d** as a 1:1.3 separable mixture of isomers.

Data for major component: isolated in 17% yield as a pale yellow oil (Found: M^+, 478.1007. $C_{22}H_{26}N_2O_5{}^{80}Se$ requires 478.1007); *m/z* (E.I.) (^{80}Se) 478 (M^+, 10%); ν_{max} (CH_2Cl_2)/cm^{-1} 1767, 1750, 1608; δ_H (300 MHz: CD_3CN) 1.15 (3H, s, CH_3), 1.20 (3H, s, CH_3), 1.30 (3H, s, CH_3), 1.31–1.90 (6H, m, 3×CH_2), 1.95 (1H, quintet, *J*=2.5 Hz, CH), 3.04 (1H, dd, *J*=16.0, 2.0 Hz, 6′β-H), 3.54 (1H, dd, *J*=16.0, 4.0 Hz, 6′α-H), 4.98 (1H, s, 2′-H), 5.22 (1H, part of AB, *J*=13.5 Hz, CH_2Ar), 5.28 (1H, part of AB, *J*=13.5 Hz, CH_2Ar), 5.29 (1H, dd, *J*=4.0, 2.0 Hz, 5′-H), 7.65 (2H, part of AA′BB′, *J*=9.0 Hz, Ar) and 8.23 (2H, part of AA′BB′, *J*=9.0 Hz, Ar); δ_C (75.5 MHz: CD_3CN) 19.6 (*C*H_3), 25.3 (*C*H_2), 29.5 (*C*H_3), 32.3 (*C*H_3), 42.0 (*C*H_2), 44.0 (*C*H_2), 46.7 ($C_{quat.}$), 48.1 (6′-*C*H_2), 50.8 (*C*H), 51.8 (5′-*C*H), 64.0 ($C_{quat.}$), 65.8 (2′-*C*H), 66.2 (*C*H_2Ar), 95.4 ($C_{quat.}$), 124.2 (CH), 129.0 (CH), 142.6 (C_{ipso}), 148.3 (C_{ipso}), 167.7 (C═O) and 169.5 (C═O).

Data for minor component: isolated in 12% yield as a pale yellow oil (Found: M^+, 478.1018. $C_{22}H_{26}N_2O_5{}^{80}Se$ requires

478.1007); *m/z* (E.I.) (^{80}Se) 478 (M^+, 9%); ν_{max} (CH_2Cl_2)/cm^{-1} 1770, 1746; δ_H (300 MHz: CD_3CN) 0.95 (3H, s, CH_3), 1.05 (3H, s, CH_3), 1.15 (3H, s, CH_3), 1.17–1.45 (6H, m, 3×CH_2), 1.94 (1H, quintet, *J*=2.5 Hz, CH), 3.07 (1H, dd, *J*=15.5, 2.0 Hz, 6′β-H), 3.43 (1H, dd, *J*=15.5, 4.0 Hz, 6′α-H), 4.71 (1H, s, 2′-H), 5.11 (1H, dd, *J*=4.0, 2.0 Hz, 5′-H), 5.25 (2H, s, CH_2Ar), 7.65 (2H, part of AA′BB′, *J*=9.0, Ar) and 8.23 (2H, part of AA′BB′, *J*=9.0, Ar). Due to the small sample available, no ^{13}C NMR data is available.

(2*S,5*R**)-7-Oxo-3,3-bis(4-methoxyphenyl)-4-selena-1-azabicyclo[3.2.1]heptane-2-carboxylic acid PNB ester 7e.** A solution of oxazolidinone **1** (0.200 g, 0.65 mmol) and selenoketone **6e** (0.256 g, 0.84 mmol) in MeCN (5 cm^3) [distilled and degassed] was heated at 80°C for 21 h in a sealed tube. The solvent was removed in vacuo and the residue was purified by flash column chromatography [60H silica gel, 1:9→1:4 EtOAc–P.E. 40–60°C] to give selenopenam **7e** (0.0.94 g, 25%) as a pale yellow oil (Found: $M+H^+$, 563.0886. $C_{27}H_{25}N_2O_7$ ^{74}Se requires 563.0887); *m/z* (C.I.) (^{80}Se) 566 ($M-H^+$, 1%); ν_{max} (CH_2Cl_2)/cm^{-1} 1772, 1751, 1606; δ_H (300 MHz: C_6D_6) 2.32 (1H, dd, *J*=16.0, 2.0 Hz, 6β-H), 2.52 (1H, dd, *J*=16.0, 4.0 Hz, 6α-H), 2.84 (3H, s, OCH_3), 2.92 (3H, s, OCH_3), 3.96 (1H, part of AB, *J*=13.0 Hz, CH_2Ar), 4.02 (1H, part of AB, *J*=13.0 Hz, CH_2Ar), 5.20 (1H, dd, *J*=4.0, 2.0 Hz, 5-H), 5.58 (1H, s, 2-H), 6.09 (2H, part of AA′BB′, *J*=9.0 Hz, Ar), 6.17 (2H, part of AA′BB′, *J*=9.0 Hz, Ar), 6.41 (2H, part of AA′BB′, *J*=9.0 Hz, Ar), 7.10 (2H, part of AA′BB′, *J*=9.0 Hz, Ar), 7.15 (2H, part of AA′BB′, *J*=9.0 Hz, Ar) and 7.43 (2H, part of AA′BB′, *J*=9.0 Hz, Ar); δ_C (75.5 MHz: C_6D_6) 49.4 (6-*C*H_2), 55.0 (O*C*H_3), 55.2 (O*C*H_3), 57.4 (5-*C*H), 65.8 (*C*H_2Ar), 68.5 (2-*C*H), 80.6 ($C_{quat.}$), 113.6 (CH), 114.4 (CH), 123.7 (CH), 129.0 (CH), 129.8 (CH), 132.2 (CH), 134.5 (C_{ipso}), 139.8 (C_{ipso}), 141.8 (C_{ipso}), 159.4 (C_{ipso}), 159.6 (C_{ipso}), 168.0 (C═O) and 168.8 (C═O). One signal due to a C_{ipso} was not observed.

(2*S,3*R**5*R**) and (2*S**,3*S**5*R**)-7-Oxo-3-methyl-3-butylthio-4-selena-1-azabicyclo[3.2.1]heptane-2-carboxylic acid PNB ester 10a.** A solution of oxazolidinone **1** (0.191 g, 0.62 mmol) and selenothio ester **9a** (0.125 g, 0.64 mmol) in MeCN (5 cm^3) [distilled and degassed] was heated at 80°C for 15 h in a sealed tube. The solvent was removed in vacuo and the residue was purified by flash column chromatography [60H silica gel, 0:1→1:4 EtOAc–P.E. 40–60°C] to afforded selenopenam **10a** (0.130 g, 45%) as a pale yellow oil and as a 1:1 mixture of isomers which were not separated. (Found: M^+, 458.0424. $C_{18}H_{22}N_2O_5S$ ^{80}Se requires 458.0414); *m/z* (E.I.) (^{80}Se) 458 (M^+, 15%); ν_{max} (CH_2Cl_2)/cm^{-1} 1778, 1750, 1608; δ_H (300 MHz: CD_3CN) 0.81 (3H, t, *J*=7.0 Hz, CH_3), 0.89 (3H, t, *J*=7.0 Hz, CH_3), 1.17–1.58 (8H, m, 4×CH_2), 1.84 (3H, s, CH_3), 2.07 (3H, s, CH_3), 2.53–2.69 (4H, m, 2×SCH_2), 3.24 (1H, dd, *J*=16.0, 2.0 Hz, 6β-H), 3.30 (1H, dd, *J*=16.0, 2.0 Hz, 6β-H), 3.70 (1H, dd, *J*=16.0, 4.0 Hz, 6α-H), 3.75 (1H, dd, *J*=16.0, 4.0 Hz, 6α-H), 4.88 (1H, s, 2-H), 4.94 (1H, s, 2-H), 5.26 (1H, part of AB, *J* 13.5 Hz, CH_2Ar), 5.28 (1H, part of AB, *J*=13.5 Hz, CH_2Ar), 5.33 (1H, part of AB, *J*=13.5 Hz, CH_2Ar), 5.35 (1H, part of AB, *J*=13.5 Hz, CH_2Ar), 5.63 (1H, dd, *J*=4.0, 2.0 Hz, 5-H), 5.65 (1H, dd, *J*=4.0, 2.0 Hz, 5-H), 7.64 (2H, part of AA′BB′, *J*=9.0 Hz, Ar), 7.68 (2H, part of AA′BB′, *J*=9.0 Hz, Ar) and 8.22 (4H, part of AA′BB′, *J*=9.0 Hz, Ar); δ_C (75.5 MHz: CD_3CN) 14.2 (*C*H_3), 14.3 (*C*H_3), 23.1 (*C*H_2), 23.2 (*C*H_2), 27.2 (*C*H_3), 31.7 (*C*H_2), 32.0 (*C*H_2), 33.7 (S*C*H_2), 34.4 (S*C*H_2), 34.8 (*C*H_3), 49.5 (6-*C*H_2), 51.3 (6-*C*H_2), 58.3 (5-*C*H), 58.4 (5-*C*H), 67.0 (*C*H_2Ar), 67.2 (*C*H_2Ar), 70.6 (2-*C*H), 72.9 (2-*C*H), 124.9 (CH), 125.0 (CH), 130.2 (CH), 130.3 (CH), 168.0 (C═O), 168.1 (C═O), 171.6 (C═O) and 171.9 (C═O) (signals due to 2-C were not observed and the aromatic carbons were not completely resolved); δ_{Se} (57.25 MHz: CD_3CN) 539.6 and 568.1.

(2*S,3*R**5*R**) and (2*S**,3*S**5*R**)-7-Oxo-3-methoxy-3-phenyl-4-selena-1-azabicyclo[3.2.1]heptane-2-carboxylic acid PNB ester 10b.** A solution of oxazolidinone **1** (0.163 g, 0.53 mmol) and selenoester **9b** (0.110 g, 0.59 mmol) in MeCN (5 cm^3) [distilled and degassed] was heated at 80°C for 13 h in a sealed tube. The solvent was removed in vacuo and the residue was purified by flash column chromatography [60H silica gel, 1:9→1:3 EtOAc–P.E. 40–60°C] to give selenopenam **10b** (0.096 g, 40%) as a 1:2 mixture of isomers (Found: M^+, 462.0337. $C_{20}H_{18}N_2O_6$ ^{80}Se requires 462.0330); *m/z* (E.I.) (^{80}Se) 462 (M^+, 4%); δ_C (75.5 MHz: CD_3CN—obtained on mixture of isomers) 47.1 (6-*C*H_2, *minor*), 51.8 (6-*C*H_2, *major*), 54.4 (O*C*H_3, *major*), 56.9 (5-*C*H, *major*), 57.8 (O*C*H_3, *minor*), 57.9 (5-*C*H, *minor*), 66.8 (*C*H_2Ar, *minor*), 66.9 (*C*H_2Ar, *major*), 75.1 (2-*C*H, *minor*), 75.3 (2-*C*H, *major*), 117.1 ($C_{quat.}$), 117.2 ($C_{quat.}$), 124.8 (CH), 124.9 (CH), 128.7 (CH), 129.7 (CH), 130.1 (CH), 130.2 (CH), 130.3 (CH), 130.4 (CH), 130.8 (CH), 137.3 (C_{ipso}), 140.3 (C_{ipso}), 143.7 (C_{ipso}), 144.5 (C_{ipso}), 149.2 (C_{ipso}), 150.6 (C_{ipso}), 167.3 (C═O), 167.4 (C═O), 171.8 (C═O) and 172.4 (C═O);

The major isomer (as determined by NMR) crystallised and the structure was determined (see text and Fig. 3 where the numbering system used corresponds to the 'penam' convention where 2-C and 3-C are switched).

Data for (2S,3R*5R*) (major) isomer:* δ_H (300 MHz: CD_3CN) 3.30 (1H, dd, *J*=16.0, 1.5 Hz, 6β-H), 3.33 (3H, s, OCH_3), 3.81 (1H, dd, *J*=16.0, 4.0 Hz, 6α-H), 4.83 (1H, s, 2-H), 5.18 (1H, part of AB, *J*=13.5 Hz, CH_2Ar), 5.30 (1H, part of AB, *J*=13.5 Hz, CH_2Ar), 5.61 (1H, dd, *J*=4.0, 1.5 Hz, 5-H), 7.32–7.37 (2H, m, Ar), 7.52 (2H, part of AA′BB′, *J*=9.0 Hz, Ar), 7.56–7.60 (3H, m, Ar) and 8.21 (2H, part of AA′BB′, *J*=9.0 Hz, Ar); δ_{Se} (57.25 MHz: $CDCl_3$) 507.8.

Data for (2S,3S*5R*) (minor) isomer* (obtained by comparison of NMR data for the mixture with that available from the pure major isomer): δ_H (300 MHz: CD_3CN) 3.17 (3H, s, OCH_3), 3.27 (1H, dd, *J*=16.0, 2.0 Hz, 6β-H), 3.75 (1H, dd, *J*=16.0, 4.5 Hz, 6α-H),), 4.62 (1H, part of AB, *J*=13.5 Hz, CH_2Ar), 4.87 (1H, part of AB, *J*=13.5 Hz, CH_2Ar), 5.07 (1H, s, 2-H), 5.74 (1H, dd, *J*=4.5, 2.0 Hz, 5-H), 7.17 (2H, part of AA′BB′ *J*=9.0 Hz, Ar), 7.26–7.31 (2H, m, Ar), 7.48–7.55 (3H, m, Ar) and 8.10 (2H, part of AA′BB′, *J*=9.0 Hz, Ar); δ_{Se} (95.35 MHz: $CDCl_3$) 396.0.

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